REMARKS

Claims 1-4, 12, 19, 20, 43, 50, 52-54, 58-61 and 68-71 were pending in the instant application. Claims 1, 2, 3, 4, 19, 20, 52, 58, 59, 63, 64, 65, and 66 have been amended. Accordingly, claims 1-4, 12, 19, 20, 43, 50, 52-54, 58-61 and 68-71 will be pending after entry of the instant amendment. For the Examiner's convenience, these claims are presented herein in Appendix A.

Support for the amended claims can be found throughout the specification and claims as originally-filed. In particular, claims 63 to 66 have been amended to correct the claim numbers. Claims 63 to 66 are now claims 68-71. Claims 2, 3, 4, and 19 have been amended to recite the proper claim dependencies.

No new matter has been added. The foregoing claim cancellations and/or amendments should in no way be construed as an acquiescence to any of the Examiner's rejections, and have been made solely to expedite prosecution of the application. Applicant reserves the right to pursue the claims as originally filed in this or a separate application(s).

Acknowledgement of Certain Claims as Allowable

Applicants gratefully acknowledge the indication by the Examiner that claim 70 is allowable.

Rejection of Claims 2-4, 12, 19, 20, 43, 52-54, and 58-61 Under 35 U.S.C. § 112, First Paragraph

The Examiner has rejected claims 2-4, 12, 19, 20, 43, 52-54, and 58-61 under 35 U.S.C. § 112, first paragraph, for the reasons previously set forth in Paper No. 9, section 7, pages 4-7. The Examiner is further of the opinion that

> the specification discloses SEQ ID NOs:3 and 4 which are mouse MEKK1 polynucleotide and polypeptide respectively while the claims encompass a broad range of sequences which contain variants and portions of the single disclosed sequences. Variations in nucleic acid sequences are known in the art to be unpredictable for the reasons previously set forth. Given the data in the specification, the broadly written claims, the unpredictable nature of the art, the general nature of the teachings drawn to isolation, selection and

identification, it appears that the artisan is left with random experimentation in order to practice the claimed invention. Random experimentation is undue. Applicant's arguments have not been found persuasive and the rejection is maintained.

Applicants traverse this rejection for the following reasons. Contrary to the Examiner's assertion Applicants disclose not only mouse MEKK molecules (SEQ ID NOs: 3 and 4), but also human MEKK molecules (SEQ ID NOs: 5 and 6) and rat MEKK (SEQ ID NO:21). Applicants are not claiming "a broad range of sequences" but rather a defined set of sequences that are at least 95% identical to the sequences set forth as SEQ ID NO:3 or a nucleotide sequence that encodes SEQ ID NO:4, and are capable of phosphorylating a mitogen-activated protein kinase kinase (MKK) protein.

Making variants is a standard technique to the ordinary skilled artisan. The Patent Office believes this to be true as evidenced by the *Interim Written Description Guidelines Training Materials* that state that ***"[t]he procedures for making variants of a known sequence [SEQ ID NO3:] are conventional in the art."*** Further, Applicants describe features of the claimed polypeptides that would allow one of skill in the art to identify molecules that are claimed. For example, Applicants have taught conserved residues between at least three MEKK1 proteins, see *e.g.*, Figures 3, 7 and 8, as well as conserved caspase cleavage sites within said MEKK1 proteins. Further, Applicants teach the existence of regulatory, catalytic, and/or apoptotic domains in the proteins encoded by the claimed nucleic acid sequences (see *e.g.*, page 17, line 3, through page 18, line 2). Applicants further teach methods of measuring the activity of the proteins encoded by the claimed nucleic acid molecules (see, *e.g.*, Examples 1-2).

To fulfill the enablement requirement under 35 U.S.C §112, first paragraph, the specification must describe how to make and use the claimed invention. However, it is well known that enablement is not precluded by the necessity for some experimentation, such as routine screening (see, e.g., *In re Wands* 8 USPQ2d 1400-1407, 1404 (CAFC, 1988)).

Based on the teachings described above and the apoptosis assays described in the Examples one of skill in the art would be able to make, isolate, and use the molecules of

the invention using only routine experimentation. Accordingly, Applicants respectfully request that he examiner reconsider and withdraw the foregoing rejection.

Objection to the Claims

The Examiner has objected to claim 58 because it depends on claims 51 which was withdrawn from consideration. Applicants have amended claim 58 as to no longer depend on claim 51.

The Examiner has further objected to claims 1-4, 19, 20 and 69 because they depend on previously canceled claims 62-65. Applicants have amended claims 1-4, 19, 20 and 69 as to depend on claims 68-70, as appropriate.

Accordingly, based on the amendments presented herein, Applicants believe that the foregoing objections have been rendered moot.

Rejection of Claims 1-4, 12, 19 and 20 Under 35 U.S.C. § 112, First Paragraph

The Examiner has rejected claims 1-4, 12, 19 and 20 under 35 U.S.C. § 112, first paragraph for the reasons previously set forth. The Examiner further is of the opinion that

> the specification, ***while being enabling for a polynucleotide comprising SEQ ID NO:3, a polynucleotide completely complementary to the full length of SEQ ID NO:3 and a method of detecting MEKK1 nucleic acid molecule comprising contacting the sample with the complete, full length complement of SEQ ID NO:3***, does not reasonably provide enablement for a complement of SEQ ID NO:3, a method for detecting the presence of MEKK1 nucleic acid comprising contacting the sample with a probe which selectively hybridizes to the nucleic acid molecule of claims 1 or 63-65 (renumbered under Rule 1.126 as claims 68-71). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Applicant traverses this rejection for the following reasons.

Applicants claims are directed to MEKK1 nucleic acid molecules that encode the full length of MEKK1 (i.e., the full length of the MEKK1 protein prior to cleavage). The Examiner admits that the specification provides enablement for a polynucleotide

comprising SEQ ID NO:3, a polynucleotide completely complementary to the full length of SEQ ID NO:3 and a method of detecting MEKK1 nucleic acid molecule comprising contacting the sample with the complete, full length complement of SEQ ID NO:3.

With regard to claims 1-4 and 12, the Examiner does not believe that the specification provides enablement for "any" complement of SEQ ID NO:3. Applicants respectfully submit that claim 1, as amended, is directed to SEQ ID NO:3, or a ***full*** complement of SEQ ID NO:3 which the Examiner has indicated above is fully enabled by the instant claims. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the foregoing rejection as it applies to claims 1-4, and 12.

With regard to claims 19-20, Applicants respectfully submits that the claims are directed to nucleic acid probe or primer which ***selectively hybridizes*** to the nucleic acid molecule identified as SEQ ID NO:3. The ordinary skilled artisan would understand that nucleic acid primers or probes that ***selectively hybridize*** to SEQ ID NO:3 do not include primers and probes that bind other nucleic acid molecules. Further, one of skill in the art would understand that primers or probes that selectively bind to SEQ ID NO:3 would not bind to other MEKK family members. Accordingly, claims 19 and 20 as pending include only nucleic acid primers and probes that ***selectively*** hybridize to SEQ ID NO:3 and not all primers and probes that bind to SEQ ID NO:3.

Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the foregoing rejection as it pertains to claims 19 and 20.

Rejection of Claims 52-54 and 71 Under 35 U.S.C. § 112, First Paragraph

The Examiner has rejected claims 52-54 and 71 under 35 U.S.C. § 112, first paragraph, because," the specification, ***while being enabling for a polynucleotide encoding a caspase-resistant MEKK1 protein***, does not reasonably provide enablement for a polynucleotide encoding a protease-resistant MEKK1 protein as claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims." (***Emphasis Added***).

In the interest of expediting prosecution, and in no way acquiescing to the validity of the Examiner's rejection, Applicants have amended claim 52 to be directed to only caspase-resistant

MEKK1 polypeptides. Accordingly, this rejection has been rendered moot by the amendments presented herein, and Applicants respectfully request that the Examiner reconsider and withdraw this rejection.

Rejection of Claim 43, and Those Depending Upon Claim 43 Under 35 U.S.C. 112, First Paragraph

The Examiner has rejected claim 43, and those claims depending upon claim 43, under 35 U.S.C. § 112, first paragraph. The Examiner believes that

> [t]he limitation of a claimed in Claim 43 drawn to a fragment having 95% sequence identity to residues 875-1493 of SEQ ID NO:4 wherein % identity is determined over the entire length of residues 875-1493 of SEQ ID NO:4 has no clear support in the specification and the claims as originally filed. A review of the specification did not reveal support. The subject matter claimed in claims 43 and the claims dependent thereon broadens the scope of the invention as originally disclosed in the specification. Applicant is invited to point specifically to page and line where support for the newly added limitation can be found.

Applicants respectfully traverse this rejection. Applicants teach beginning on page 6, that active fragments of MEKK1 are intended to be included in the invention. Specifically, Applicants teach at page 6, lines 31-34 of the specification, a preferable active fragment having "an amino acid sequence having at least 95% homology to an amino acid sequence consisting of about amino acids 875-1493 of SEQ ID NO:4." Support for the claims that depend from claim 43 can be found at page 6, lines 31-34 of the specification. Further, methods of performing global sequence alignments are well know in the art and are described in the instant specification. Applicants disclose two algorithms that a skilled artisan could use to align polypeptide or nucleic acid sequences (see, page 14, lines 17-32). Moreover, Applicants provide exemplary global amino acid sequence alignments in Figures 3, 7 and 8 of the instant application.

Based on the above-identified support in the specification, and the level of skill of the ordinary skilled artisan, Applicants respectfully request that the Examiner reconsider and withdraw the foregoing rejection.

Rejection of Claim 52, and Those Depending Upon Claim 52 Under 35 U.S.C. 112, First Paragraph

The Examiner has rejected claim 52, and those claims depending upon claim 52, under 35 U.S.C. § 112, first paragraph, because, "the specification does not contain a written description of the claimed invention." Specifically the examiner is of the opinion that

> [t]he limitation of a claimed in Claim 52 drawn to a sequence with at least 95% identity to SEQ ID NO:4 wherein % identity is determined over the entire length of SEQ ID NO: 1... after an amino acid equivalent to amino acid 874 of SEQ ID NO:4, has no clear support in the specification and the claims as originally filed. A review of the specification did not reveal support. The subject matter claimed in claims 52 and the claims dependent thereon broadens the scope of the invention as originally disclosed in the specification. Applicant is invited to point specifically to page and line where support for the newly added limitation can be found.

Applicants respectfully traverse this rejection. Applicants teach beginning on page 8, that the invention provides protease resistant forms of MEKK1. Specifically, Applicants teach at page 8, lines 8-19 of the specification

> the invention ***provides an isolated nucleic acid molecule encoding a protease-resistant MEKK1 protein***, wherein the protease resistant MEKK1 protein comprises an amino acid sequence having at least 75% homology to the amino acid sequence of SEQ ID NO:4 and at least one codon of the nucleic acid molecule encoding an amino acid equivalent to at least one of amino acids 871-874 of SEQ ID NO:4 is mutated ***such that the encoded MEKK1 protein is resistant to proteolysis by a caspase after an amino acid equivalent to amino acid 874 of SEQ ID NO:4***. Preferably, the MEKK1 protein comprises an amino acid sequence having at least 85% homology to the amino acid sequence of SEQ ID NO:4. ***More preferably, the MEKK1 protein comprises an amino acid sequence having at least 95% homology to the amino acid sequence of SEQ ID NO:4***

In addition to the support identified above on page 8 of the specification, Applicants teach how one of skill in the art would perform a global sequence alignment (see page 9 above). Accordingly, Applicants have provided support in the specification for claim 52, and respectfully request that the Examiner reconsider and withdraw the foregoing rejection.

Rejection of Claim 53, and Those Depending Upon Claim 53 Under 35 U.S.C. 112, First Paragraph

The Examiner has rejected claim 53, and those claims depending upon claim 53, under 35 U.S.C. § 112, first paragraph, because, "the specification does not contain a written description of the claimed invention." Specifically, the Examiner is of the opinion that

> [t]he limitation claimed in Claim 53 drawn to at least one codon is mutated to encode an alanine residue has no clear support in the specification and the claims as originally filed. A review of the specification did not reveal support. The subject matter claimed in claim 53 broadens the scope of the invention as originally disclosed in the specification. Applicant is invited to point specifically to page and line where support for the newly added limitation can be found.

Applicants respectfully traverse this rejection. Applicants teach beginning on page 8, that the invention provides protease resistant forms of MEKK1. Specifically, Applicants teach at page 7, lines 10-12 of the specification that, "***one or more of the amino acids corresponding to 871-874 of SEQ ID NO:4*** or to 681-684 of SEQ ID NO:6 ***can be mutated to, for example, alanine residues.***"

Accordingly, Applicants have provided support in the specification for claim 53, and respectfully request that the Examiner reconsider and withdraw the foregoing rejection.

Rejection of Claim 54, and Those Depending Upon Claim 54 Under 35 U.S.C. 112, First Paragraph

The Examiner has rejected claim 54, and those claims depending upon claim 54, under 35 U.S.C. § 112, first paragraph, because," the specification does not contain a written description of the claimed invention." Specifically, the Examiner is of the opinion that

> [t]he limitation claimed in Claim 54 drawn to each one codon is mutated to encode an alanine residue has no clear support in the specification and the claims as originally filed. A review of the specification did not reveal support. The subject matter claimed in claims 54 broadens the scope of the invention as originally disclosed in the specification. Applicant is invited to point

> specifically to page and line where support for the newly added limitation can be found.

Applicants respectfully traverse this rejection. Applicants have provided support for claim 54 in claim original claim 36, and accordingly, respectfully request that the Examiner reconsider and withdraw the foregoing rejection.

Rejection of Claims 52-54 and 71 Under 35 U.S.C. 112, Second Paragraph

The Examiner has rejected claims 52-54 and 71 under 35 U.S.C. § 112, second paragraph as, "being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." Specifically, the Examiner states that

> [c]laims 52-54, 71 are indefinite because claim 52 is confusing in the recitation of "an amino acid equivalent", is Applicant claiming a conservative substitution that is mutated? Is Applicant claiming a constituent that is not an amino acid?. The claim is further confusing because the preamble of the claim is drawn to a "protease resistant MEKK1 protein while the body of the claim is drawn only to resistance to a caspase? It is unclear whether Applicant is claiming a caspase resistant protein or whether the protein is meant to be resistant to all proteases by mutation of at least one of the cited encoded amino acids?
> Claim 71 is confusing because it is unclear whether claim 71 is drawn to a nucleic acid which encodes SEQ ID NO:4 or whether the claim is drawn to SEQ ID NO:4, wherein at least one codon encoding amino acids 871-874 are mutated.

Applicants respectfully traverse the foregoing rejection. Applicants respectfully point out that the Examiner has misread the instant claims. They instant claims are not claiming "an amino acid equivalent," but rather are limited to a mutant nucleic acid molecule in which "one codon of the nucleic acid molecule encoding an amino acid equivalent to at least one of amino acids 871-874 of SEQ ID NO:4 is mutated such the encoded MEKK1 protein is resistant to proteolysis." These claims are directed to a nucleic acid molecule that encodes a polypeptides in which one of the amino acid residues that is equivalent to the amino acid residues present at positions 871-874 of SEQ ID NO:4 is substituted with any other amino acid. Methods of performing global sequence alignments are well known in the art, and further, are taught in the instant specification (see, for example, page 14, line 17-32 of the specification). An ordinary

skilled artisan would understand that the instant claim is directed to nucleic acid molecules that encode a polypeptide with a mutated amino acid residue in one or more of the positions equivalent to positions 871-874 of SEQ ID NO:4. Based on the disclosure and the level of knowledge of one of skill in the art, the ordinary skilled artisan would understand claim 52 to be clear and definite.

Applicants have amended claim 52 such that the preamble and the body of the claim are directed to caspase resistant polypeptides. Accordingly, this portion of this § 112, second paragraph rejection is rendered moot.

Lastly, the Examiner has indicated that claim 71 is confusing. Applicants have amended claim 71 to more clearly define what is being claimed. Applicants believe that the amended claim more accurately indicate that Applicants are claiming an isolated nucleic acid molecule that encodes SEQ ID NO:4, wherein at least one of the codons encoding amino acid residues 871-874 of SEQ ID NO:4 is mutated.

Accordingly, based on all of the above, Applicants respectfully request that the Examiner reconsider and withdraw this § 112, second paragraph rejection.

Rejection of Claims 1, 2, 4, 12, 19, 20, 43, 50, 58, and 60 Under 35 U.S.C. 102(b)

The Examiner has rejected claims 1, 2, 4, 12, 19, 20, 43, 50, 58, and 60 under 35 U.S.C. 102(b) as being anticipated by WO 94/241159. The Examiner states that

> WO 94/241159 teaches a nucleic acid molecule which is 99.9% identical to 61.8% of SEQ ID NO:3 (see sequence search us-09-403-075-3.rng, result 6). The complete complement of which would be instantly known to those involved in the art and which would be partially complementary to SEQ ID NO:3. The reference teaches the polynucleotide in a vector, in a host cell, methods of producing a protein, methods of detecting the polynucleotide and corresponding kits (see pages 50-59). Further, the nucleic acid sequence encodes an active fragment of with 100% identity to residues 875-1493 (see sequence search us-09-403-075-4.p2n.rng, p. 15-17) and which therefore inherently has the claimed functional property which due to the degeneracy of the genetic code encodes the same amino acid sequence as nucleotides 2637-4493 of SEQ ID NO:3 as well as expression vectors and host cells containing the expression vector as set forth above (see sequence search us-09-403-075-3.rng, result 6 and us-09-403-075-4.p2n.rng, p. 15-17). All of the limitations of the claims are met.

The Examiner further states that

> the specification does not define "complement thereof", therefore, *it is assumed for examination purposes that the claimed complement thereof is not the complete full length complement but rather a nucleic acid molecule that is partially complementary* to the nucleotide sequence of SEQ ID NO:3.

Applicants respectfully traverse the foregoing rejection. Applicants believe that the Examiner has misinterpreted the pending claims as being directed to a complement of some portion of the full length of the sequence disclosed. Applicants claims are directed to SEQ ID NO:3 or a complement thereof, or a nucleic acid molecule that encodes SEQ ID NO:4 or a complement thereof. As described above, Applicants claims are directed to nucleic molecules that are complementary to the full length of SEQ ID NO:3, or to the full length of the nucleic acid molecule that encodes SEQ ID NO:4.

WO 94/241159 discloses fragment of SEQ ID NO:3 with is only 61.7% of the length of SEQ ID NO:3 (as evidenced by the Examiner's alignment attached to paper 12). Accordingly, the instant claims are not anticipated by WO 94/241159 since WO 94/241159 only discloses a fragment of the molecule of the instant invention.

Rejection of Claims 1 and 20 Under 35 U.S.C. 102(b)

The Examiner has rejected claims 1 and 20 under 35 U.S.C. 102(b) as being anticipated by Boehringer Mannheim Biochemicals, 1994 Catalog, p. 93. The Examiner states that

> [t]he Boehringer Mannheim teaches a kit and instructions for use thereof comprising random primers that encompass all possible 6-nucleotide sequences (see page 93, Catalog No. 1034 731/1006 924), and therefore a subset of the random primers would include the complement of the claimed polynucleotide. Since the specificity of selective hybridization depends upon hybridization, since a subset of the primers would hybridize completely, these primers are clearly selective for those sequences.

Applicants have stated above that the instant invention is directed to compliments of the full length MEKK1 molecules disclosed in the specification. The six nucleotide primers disclosed in the Boehringer Mannheim Catalog are at most 0.14% the length of the disclosed molecules. Accordingly, the small oligonucleotide sequences disclosed in the Boehringer Mannheim catalog do not anticipate the

invention as claimed. Accordingly, Applicants respectfully request that the examiner reconsider and withdraw this rejection.

Rejection of Claims 1 and 3 Under 35 U.S.C. 103

The Examiner has rejected claims 1 and 3 under 35 U.S.C.103 as being obvious over WO 94/24159, and further in view of US Patent No. 5,968,781.

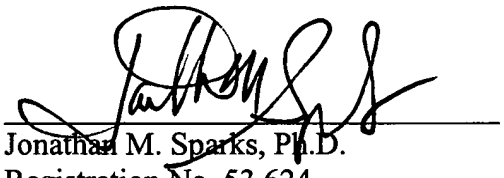
The teachings of WO 94/24159 are described above. US Patent No. 5,968,781 teaches recombinant molecules comprising a polynucleotide encoding a protein which further comprises nucleotide sequences encoding a histidine tag inserted into the 5' terminus or 3' terminus of the gene and further teaches that the tag prevents degradation of the recombinant protein and facilitates purification of the protein by histidine tag affinity column as a metal chelating affinity column.

Applicants have described the deficiencies of WO 92/24159 to anticipate the instant claims. US Patent No. 5,968,781 fails to make up for the deficiencies in WO 92/24159. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the foregoing rejection.

CONCLUSION

Reconsideration and allowance of all the pending claims is respectfully requested. If a telephone conversation with Applicants' Attorney would expedite prosecution of the above-identified application, the Examiner is urged to call the undersigned at (617) 227-7400.

Respectfully submitted,



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APPENDIX A

1. (Currently Amended) An isolated nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO:3 or a full complement thereof.

2. (Currently Amended) The nucleic acid molecule of any one of claims 1 and 68-70, further comprising vector nucleic acid sequences.

3. (Currently Amended) The nucleic acid molecule of any one of claims 1 and 68-70, further comprising nucleic acid sequences encoding a heterologous polypeptide.

4. (Currently Amended) A host cell which contains the nucleic acid molecule of any one of claims 1 and 68-70.

12. (Previously Presented) A method for producing a MEKK1 protein comprising culturing the host cell of claim 4 under conditions in which the nucleic acid molecule is expressed.

13-18. (Canceled)

19. (Currently Amended) A method for detecting the presence of a MEKK1 nucleic acid molecule in a sample comprising:

a) contacting the sample with a nucleic acid probe or primer which selectively hybridizes to the nucleic acid molecule of any one of claims 1 and 68-70; and

b) determining whether the nucleic acid probe or primer binds to a nucleic acid molecule in the sample to thereby detect the presence of a MEKK1 nucleic acid molecule in the sample.

20. (Currently Amended) A kit comprising a compound which selectively hybridizes to the MEKK1 nucleic acid molecule of any one of claims 1 and 68-70 and instructions for use.

21-42. (Canceled)

43. (Previously Presented) An isolated nucleic acid molecule which encodes an active fragment of MEKK1 that mediates apoptosis, said fragment having 95% sequence identity to residues 875-1493 of SEQ ID NO:4, wherein % identity is determined over the entire length of residues 875-1493 of SEQ ID NO:4.

50. The nucleic acid molecule of claim 43, which consists of nucleotides 2637-4493 of SEQ ID NO:3, or a nucleotide sequence that, due to the degeneracy of the genetic code, encodes the same amino acid sequence as nucleotides 2637-4493 of SEQ ID NO:3.

52. (Currently Amended) An isolated nucleic acid molecule encoding a caspase-resistant MEKK1 protein, wherein the caspase-resistant MEKK1 protein comprises an amino acid sequence having at least 95% identity to the amino acid sequence of SEQ ID NO:4, wherein % identity is determined over the entire length of SEQ ID NO:4, and wherein at least one codon of the nucleic acid molecule encoding an amino acid equivalent to at least one of amino acids 871-874 of SEQ ID NO:4 is mutated such the encoded MEKK1 protein is resistant to proteolysis by a caspase after an amino acid equivalent to amino acid 874 of SEQ ID NO:4.

53. (Previously Presented) The nucleic acid molecule of claim 52, wherein at least one codon is mutated to encode an alanine residue.

54. (Previously Presented) The nucleic acid molecule of claim 52, wherein each codon is mutated to encode an alanine residue.

58. (Currently Amended) An expression vector comprising the nucleic acid molecule of any one of claims 43, 50 and 52.

59. (Currently Amended) An expression vector comprising the nucleic acid molecule of claims 53 or 54.

60. (Previously Presented) A host cell containing the expression vector of claim 58.

61. (Previously Presented) A host cell containing the expression vector of claim 59.

68. (Currently Amended) An isolated nucleic acid molecule which encodes a protein having at least 95% identity to the sequence set forth as SEQ ID NO:4, wherein % identity is determined over the entire length of SEQ ID NO:4 and wherein the protein is capable of phosphorylating a mitogen-activated protein kinase kinase (MKK) protein.

69. (Currently Amended) The nucleic acid molecule of claim 68, wherein the encoded protein is capable of phosphorylating a MKK protein selected from the group consisting of MKK1, MKK2, MKK3 and MKK4.

70. (Currently Amended) An isolated nucleic acid molecule which encodes a protein comprising the amino acid sequence of SEQ ID NO:4.

71. (Currently Amended) The isolated nucleic acid molecule of claim 52, wherein at least one codon encoding amino acid residues 871-874 of SEQ ID NO:4 is mutated.